Statistical Consult for NDA 21-229

NDA 21-229
Name of Drug: Prilosec (omeprazole)
Applicant: Proctor and Gamble Co.
Indication: Treatment of Heartburn
Documents Reviewed: Electronic documents for use studies (003, 014, 022, 067, 091) submitted by sponsor on 1/27/00 and 4/25/00.
Medical Reviewer: Dr. Ling Chin and Dr. Daiva Shetty
Statistical Consultant: Laura Lu, Ph.D.
Date of Review: 9/11/00

I. Introduction

The sponsor conducted a total of 5 OTC use studies (Studies 003, 014, 022, 067, 091) to assess consumer compliance. These are uncontrolled studies with one-arm (omeprazol). Study 003 was the primary actual use study with 1514 patients recruited and 1093 patients participated. The primary objective of these studies was to characterize the usage patterns/dosing compliance of omeprazole magnesium when used according to proposed label instructions under naturalistic OTC conditions. Per Dr. Ling Chin's request, this statistical consult provides comments for Study 003. Comment #3 also applies to Studies 022 and 067.

II. Statistical Comments

1. Confidence Intervals

The primary information for compliance provided by the sponsor was the consistency (with label in terms of dosing compliance) rates among the patients who took at least one dose of medication and had complete data. Confidence intervals are more informative than the a single rate estimation by providing a range for the estimation rate based on estimation error. Therefore, this reviewer presents the 95% confidence intervals for the consistency rate in overall and prevention/relief patient populations for the actual use study 003 in Table 1 below. According to the company, a total of 815 patients had compliance status (consistent or inconsistent) with 812 of these from the completer's group and 3 of these from the incompleter's group. But it is not sure how these 815 patients were associated with the detailed patient disposition groups presented in Table 1a in Appendix A.

Table 1. Point Estimation and Confidence Intervals for Consistency Rate (Study 003)

	Prevention Any Time (N = 36)	Prevention 1 hr Before (N = 28)	Dual Prevention (N = 13)	Relief (N = 316)	Prevention And Relief (N = 422)	Overall (N = 815)
Consistency (n (%))	9 (25%)	9 (32%)	7 (54%)	254(80%)	228 (54%)	507 (62%)
95% Confidence Interval	(11%, 39%)	(15%, 49%)	(27%, 81%)	(76%, 84%)	(49%, 59%)	(59%, 65%)

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2. Lost-to-Follow-up Patients

In Study 003, a total of 210 patients were lost to follow-up (see Table 1a in Appendix A) without returning the product use journal, so no information was available in actual use pattern. Among the baseline characteristics, frequency of heartburn during day time in the past, frequency of heartburn during night time in the past, Rx medication use (whether Rx medication was used for heartburn before), and medication factor (whether medication was a factor contributing to heartburn in the past) were strongly associated with consistency rate (p=0.001). Detailed results presented in Tables a2-a5 in Appendix A show that consistency rate decreases as the frequency of heartburn increases, and the consistency rate is lower among patients who used Rx heartburn medication before and among patients whose heartburn was contributed by use of medication. To assess the potential difference in consistency rates among the lost-to-follow-up patients and the completers, the distribution of heartburn frequency, Rx medication use and medication factor among the completers and lost-to-follow-up patients were compared in Tables 2-5 below. Tables 2 and 3 below show that the lost-to-follow-up patients tend to have heartburn less frequently compared with the completer group. Tables 4-5 show that the proportion of patients who used Rx medication before and the proportion of patients whose heartburn was contributed by use of medication were less among lost-to-follow-up patients than that of the completer group. So based on association between baseline characteristic and consistency rate, there is no evidence showing that the consistency rate in the lost-to-follow-up patients were lower than that in the completer group. However, since the consistency rate could be influenced by unobserved factors such as reason for taking the medication, there is still chance that the consistency rate in the lost-to-follow-up group is lower than that in the completer's group.

Table 2. Distribution of Frequency of Heartburn During Daytime (Study 003)

Patient Population	Frequency of Heartburn During Daytime				
	Rarely	1	2-3	4-5	>=6
Completer (N=874)	170 (19.5%)	174 (19.9%)	319 (36.5%)	101 (11.6%)	110 (12.6%)
L-T-F-U* (N=210)	83 (39.5%)	52 (24.8%)	57 (27.1%)	11 (5.2%)	7 (3.3%)

*: Lost-to-follow-up patients

Table 3. Distribution of Frequency of Heartburn During Nighttime (Study 003)

Patient Population	Frequency of Heartburn During Nighttime				
	Rarely	1	2-3	4-5	>=6
Completer (N=874)	298 (34.1%)	160 (18.3%)	267 (30.6%)	77 (8.8%)	72 (8.2%)
L-T-F-U* (N=210)	103 (49.1%)	47 (22.4%)	40 (19.1%)	15 (7.1%)	5 (2.4%)

*: Lost-to-follow-up patients

Table 4. Distribution of Rx Medication Use (Study 003)

Patient Population	Rx Medication Use	
	Yes	No
Completer (N=874)	95 (10.9%)	779 (89.1%)
L-T-F-U* (N=210)	8 (3.8%)	202 (96.2%)

*: Lost-to-follow-up patients

Table 5. Distribution of Medication Factor (Study 003)

Patient Population	Medication Factor	
	Yes	No
Completer (N=874)	26 (3.0%)	848 (97.0%)
L-T-F-U* (N=210)	0 (0.0%)	210 (100.0%)

*: Lost-to-follow-up patients

3. Analyses Based on Predominant Use Groups

Consistency rates were also provided by predominant use groups (where predominant use is defined as using the study medication more than 50% of the time for anyone of the three reasons for use: 1) predominant Prevention-Any-Time users, 2) predominant Prevention-1-Hour-Before users, 3) predominant Relief users, and 4) no predominant use (includes those subjects who did not use the study medication more than 50% of the time for any one of the three reasons for use)). Since the analyses based on predominant use groups were not prespecified and there is no clear rationale for this reclassification, judgement should be based on the results from the prespecified analyses based on strict prevention/relief groups.

Laura Lu

Mathematical Statistician

Concur:

9/13/00

Stan Lin, Ph.D.
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HFD-180/Walsh
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HFD-560/Div. File
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Appendix A

Table 1a. Patient Disposition in Study 003

Reason for Discontinuation	N
Received Study Medication and Product Use Journal	1093
Completed Study	874
Took at Least 1-Dose Medication	822
Did Not Take Medication	52
Did Not Complete Study	219
Adverse Event	4
Subject Reconsidered/Withdrew Consent	4
Lost to Follow-Up	210

Table 2a. Frequency (Daytime) BY Consistency Status

Heartburn History: Frequency During Daytime
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
2-3	109	202	311
	13.37	24.79	38.16
	35.05	64.95	
	35.39	39.84	
4-5	50	50	100
	6.13	6.13	12.27
	50.00	50.00	
	16.23	9.86	
>=6	75	32	107
	9.20	3.93	13.13
	70.09	29.91	
	24.35	6.31	
ONCE	37	118	155
	4.54	14.48	19.02
	23.87	76.13	
	12.01	23.27	
RARELY	37	105	142
	4.54	12.88	17.42
	26.06	73.94	
	12.01	20.71	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

Table 3a. Frequency (Night) BY Consistency Status

Heartburn History: Frequency During Night
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
2-3	110	145	255
	13.50	17.79	31.29
	43.14	56.86	
	35.71	28.60	
4-5	32	44	76
	3.93	5.40	9.33
	42.11	57.89	
	10.39	8.68	
>=6	47	25	72
	5.77	3.07	8.83
	65.28	34.72	
	15.26	4.93	
ONCE	38	109	147
	4.66	13.37	18.04
	25.85	74.15	
	12.34	21.50	
RARELY	81	184	265
	9.94	22.58	32.52
	30.57	69.43	
	26.30	36.29	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

Table 4a. Rx Medication Use By Consistency Status

Heartburn History: Rx Medication Use (Y=Yes, N=No)
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
N	253	471	724
	31.04	57.79	88.83
	34.94	65.06	
	82.14	92.90	
Y	55	36	91
	6.75	4.42	11.17
	60.44	39.56	
	17.86	7.10	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

Table 5a. Medication Factor By Consistency Status

MEDICAT(Heartburn Factor: Medication, 1=Yes, 2=No)
Consistency (Y=Yes, N=No)

Frequency Percent Row Pct Col Pct	N	Y	Total
1	18	7	25
	2.21	0.86	3.07
	72.00	28.00	
	5.84	1.38	
2	290	500	790
	35.58	61.35	96.93
	36.71	63.29	
	94.16	98.62	
Total	308	507	815
	37.79	62.21	100.00

P-value from Chi-Square Test: 0.001

NDA 21-229
HFD-560 Division Files
HFD-180 Division Files
HFD-560 Ganley/Katz/ Shetty/Chin/Cothran
HFD-180 Walsh